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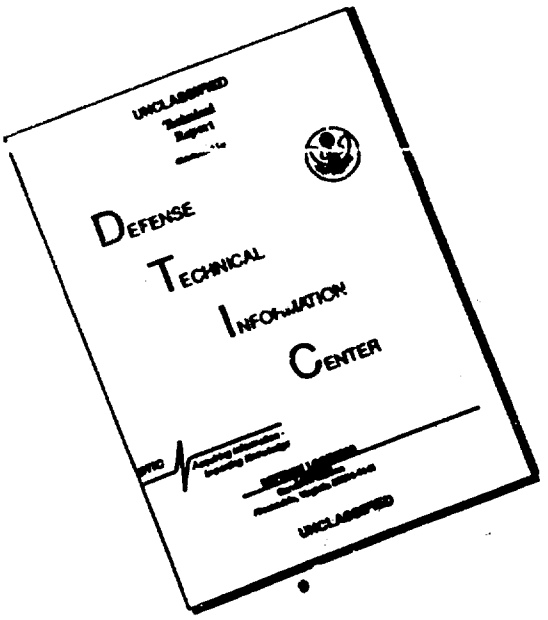

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THE ROLE OF AUTOANTIGENS AND AUTOANTIBODIES IN THE PATHOGENESIS OF INTERNAL DISEASES

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Recently, more and more attention is being directed to autoantibodies and autoantigens, which have more than a little importance in the pathogenesis of certain diseases. Not only bacteria, viruses, toxins and other foreign substances can act as antigens but so also can appropriately altered denatured proteins of the body.

It has been known for a long time that in certain cases the agglutination of the erythrocytes of autogenous serum is obtained in connection with the appearance of cold autoagglutinins. At the present time, the existence of leucolysis, leucoagglutinins, leucoopsonins, thrombocytoagglutinins and other autoantibodies has been established.

The signs of autoimmunization were first discovered by I. I. Mechnikov and his pupil, I. Metal'nikov, at the end of the nineteenth century. After injecting the spermatozoa of guinea pigs into their abdominal cavities antibodies were obtained which were called spermotoxins which were capable of immobilizing the spermatozoa. Later, similar investigations were carried out by Fesenger /?/, Landsteiner and others. After injecting experimental animals with an extract of their own livers anti-hepatic globulins were obtained. Thus, it is possible to obtain anti-leucocytic, anti-hepatic and other antibodies.

The organism "protects itself" with autoimmune substances against its own cells and tissues, and destroys them. Under appropriate conditions, opposites existing in the organism

itself attain the level of antagonistic contradictions, and a normal physiological process is converted into a pathological one. The organism begins to fight against its own organs and systems.

New investigations are showing that autoantibodies, like ordinary antibodies, have their own respective specifities. By means of radioactive isotopes Presman established the fact that the anti-hepatic globulins are retained in the kidneys up to 20 days. Anti-pulmonary antibodies basically concentrate in the lungs, but they occur in the kidneys also, in smaller quantities. These data still do not prove that the antibodies are not strictly specific, because various substances enter the kidneys when they are excreted from the organism. The experiments of M. Perrault and his colleagues are more convincing. According to their data, cardiac serum in experimental animals accumulates in large quantities not only in the heart but also in the liver; brain antiserum accumulates not only in the brain but also in the heart or liver. V. Baumgartner believes that the antibodies elaborated against microorganisms are capable of combining with erythrocytes also.

The opinion that antibodies are not strictly specific is confirmed also by clinical observations. In diseases of the [illegible] produced by autoaggressors changes are found in the [illegible], and in certain kidney diseases, involvements of a number of other organs. A. Beykert described a case of lupus erythematosus where the disease had for the first three years manifested itself in the form of symptoms of hemolytic anemia. In our hospital, in 1952, we had a patient with arthralgias of unknown etiology. In 1955, clear-cut signs of lupus erythematosus appeared, and in 1956, severe thrombocytopenia (9000). The syndromes mentioned are united by a community of pathogenetic factors. In the first case, the anti-erythrocytic antibodies predominated first; later, the changes in the connective tissue. In the second case, the disease began with changes in the collagenous tissue, and after four years antithrombocytic globulins appeared. Study of the mechanism of development of the disease makes it possible to establish the connection between various syndromes and diseases. Through the participation of autoagressors a general rule operates in the pathogenesis of a disease, which afflicts the entire organism rather than individual organs.

Concerning the sites of formation of the antibodies, certain authors assert that the synthesis of immune globuline

occurs basically in the red pulp of the spleen. However, the removal of this organ in diseases caused by autoantibodies is not always crowned by success. We must agree, as A. Lemaire points out, that the cells of the reticulo-endothelial system, lymphocytes and plasma cells are capable of elaborating antibodies. A. Deloner believes that the cells of the connective tissue can produce immune globulins.

The chemical composition of the antibodies has been as yet little elucidated. It is known that they belong to the group of globulins, to their beta- and gamma-fractions. Still less is known of the chemical composition of antigens, which, in addition to heterogeneous protein, can be any chemical substance which in combination with proteins gives so-called haptenes; the proteins of the organism itself acquire the properties of antigens if its composition is appropriately altered.

There are many diseases in the development of which the autoantigens participate. In the literature, a cold-autoagglutinin disease has been described which is characterized by hemolytic anemia and by disturbances of the peripheral capillary circulation, which induces a marked cyanosis of the fingers, tip of the nose, helices of the ear and even the face. In the summer, the patients are healthy; in the winter, they develop anemia, jaundice and cyanosis. Autoagglutination of the erythrocytes occurs immediately after the taking of blood for examination and disappears on heating to 37°. V. Baumgartner established by means of capillaroscope that after cooling of the fingers a granular agglutination of the erythrocytes is obtained and a disturbance of the capillary circulation, which disappears on heating.

Many diseases which have long been known, and the etiology and pathogenesis of which have not as yet been adequately clarified, belong into the group of diseases produced by autoaggressors. In this group are a series of diseases of the circulatory organs, like acquired hemolytic anemia, acute leukemia, leukopenia and thrombocytopenia. The autoantigens participate in the development of nephritis, cirrhosis of the liver, necrosis of the pancreas, post-infectious encephalitis, rheumatic fever, periarteritis nodosa, lupus erythematosus, etc.

All the changes in the organism during subacute bacterial endocarditis cannot be explained simply by the effect of infection. Schottmueller's opinion that the Streptococcus viri-

dans is the specific causal agent of bacterial endocarditis is at the present time disputed by many authors. Certain investigators emphasize the community of Streptococcus viridans with microbes of the oral cavity, particularly with Streptococcus salivarius, which under definite conditions can become the source of bacterial endocarditis. According to the data of Friedman and Kefar [?], this streptococcus when injected into the blood of a healthy person, even in large quantities, is destroyed by leucocytes. Only as the result of sensitization of the organism and change of its reactivity does an ordinary infection become dangerous. In subacute bacterial endocarditis, as Hennemann mentions, autoagglutinins arise.

The opinion that the autogenous antigens have more than a little role in the pathogenesis of subacute bacterial endocarditis and rheumatic fever deserves serious attention. Participation of the autogenous antigens in the development of the diseases mentioned is confirmed by the Coombs reaction, which in rheumatic fever, according to the data in the literature, is positive in 75 percent of the patients.

Certain experiments of foreign authors, which should not have been done on people, carried out with the aim of proving the existence of a specific virus, do not give us anything on which to ground an infection theory of rheumatic fever. Thus, Friedman and his colleagues took blood from patients during the acute period of rheumatic fever, and after filtering the serum obtained through a Berkefeld candle, injected it intravenously into the same patients during a period of recovery; in six of the seven patients symptoms of the original disease appeared. The same serum, injected intravenously into other patients with rheumatic fever during period of quiescence of the process produced a mild general reaction in only one out of four patients. It is understood that the agent which basically produces a reaction in only those patients from whom it is obtained belongs to the group of autoaggressors and not to the viruses.

G. D. Zalesskiy sensitized guinea pigs with a single subcutaneous injection of 0.1 cubic centimeter of serum from the blood of rheumatic fever patients; after three weeks he desensitized them with respect to the proteins of normal human serum, and, after the resolving injection in the cardiac cavity of blood taken from patients during the acute period of rheumatic fever, he obtained a stormy anaphylactic reaction in 20 out of 22 guinea pigs. As a result of these

experiments he draws the conclusion that a specific antigen is contained in the blood serum of patients, which, in the author's opinion, is a virus. However, autogenous antigens can also give the same anaphylactic reaction.

In connection with the discovery of the autoantigens additions have been made to our knowledge of the mechanism of action of external factors, including also upper respiratory diseases. In 1784, Callan's theory of the upper respiratory factor as a cause of rheumatic fever appeared. R. Pel and G. Wescot noted that 90.4 percent of patients with acute rheumatic fever are sensitive to marked changes in the weather. It is widely known that patients with rheumatic fever feel the weather changes, and they are afraid of chills and drafts. Of our 200 patients 28 percent associated the onset of the rheumatic fever attack with the action of low temperature. According to the data of various authors, the attacks most often begin in the late autumn and early spring. We studied the frequency of cases of rheumatic fever in connection with the meteorological factors in 1927-1935. It turned out that the greatest number of cases in Lithuania occur in December and March, when there is a low temperature, high relative humidity and strong winds. Rheumatic fever attacks begin comparatively rarely in the summer in the presence of the high temperature, low relative humidity and mild winds.

I. A. Kassirskiy points out that the physico-chemical condition of the cells and tissues is altered from the effect of cold on the mucous membranes, and under these conditions certain microbes (pneumococci, streptococci) acquire virulence and become more active. According to the opinion of I. V. Vorob'yeva, it is not the chilling of the body in many cases but rather the upper respiratory disease of the tonsils and upper respiratory passages which occurs after it which is the cause of the rheumatic fever.

Cold can act through the nervous system, particularly in the presence of a disturbance of the heat-regulatory mechanisms. As our colleague I. B. Danis noted, in those suffering from rheumatic fever the reaction to stimulation by cold is paradoxical. The absence of adequate reactions to the stimulus induces its harmful effect.

Aside from the disturbance of heat regulation and the decrease in the resistance of the body, the formation of cold auto-antibodies apparently occurs also. Sometimes, the patients complain of edema of the fingers in the presence

of slight cooling of them, and of cyanosis of them during the winter period; such an inverted reaction can occur only in connection with autogenous sensitization.

It has not as yet been adequately clarified as to which are the diseases in the pathogenesis of which the autoantibodies participate. Under the influence of the attractive theory of autoantigens and autoantibodies certain authors refer more and more nosologic entities to this group of diseases. They even explain certain phenomena of senile involution through the action of the autoaggressors. In connection with the prolonged action of the harmful agents, the altered organs become "foreign" to the organism itself. However, many non-infectious diseases occur through repeated and prolonged traumata by various pathogenic environmental stimuli rather than in connection with the action of any single factor as occurs in experimental cases. In studying pathogenesis, the number of diseases caused only by streptococci, endocrine glands, autoantigens or any other isolated factors should not be exaggerated, because pathological changes in the majority of cases are induced by a combination of several causes. Without exaggerating the role of the autoimmune mechanisms a study should be made as to what place they occupy among the other agents in the development of the complex pathological process.

In studying the causes of the formation of autoantibodies many disputable problems need to be dealt with. Certain foreign authors believe that under the influence of the streptococcous or other, even slightly pathogenic infection, the tissues of the organism acquire the properties of antigens. There is no doubt of the fact that infection sometimes contributes to the development of immune globulins.

Under normal conditions, the absorption of agglutinins by erythrocytes occurs at a temperature of from 0 to 5°. In pathological cases, the temperature limit of the formation of agglutinins is extended up to 30° and higher, that is, it reaches the temperature of the peripheral portions of the organism. It is well known that trypanosomiasis is accompanied by a high titer of cold antibodies, and in these cases nobody disputes the influence of the parasite on the development of the agglutinins. However, it would be incorrect to suppose that the capacity of producing structural changes in the protein is proper only to microorganisms. G. A. Alekseyev points out that the role of syphilis in the etiology of paroxysmal cold Hemoglobinuria suggested by the

old authors is exaggerated.

It may be supposed that various strong stimuli under appropriate conditions contribute to the development of biochemical changes in the cells and a sensitization of the organism to its own denatured protein.

In burns, a mass destruction of cells occurs, in the process of which changes in their proteins occur. According to the data of Yu. N. Orlenko, the percentage of transfusion reactions in transfusing burn patients with glucose plasma reaches 18.7. In cases of acquired hemolytic disease, heat autoagglutinins are known. Thus, low as well as high temperature can produce autoantibodies.

V. N. Kraniskaya-Ignatova and Z. G. Arlozorov point out that autoimmune antibodies are formed sometimes in patients in the presence not only of thermal but also of traumatic necrosis. In three of our patients a rheumatic fever attack began after trauma to the joint of the leg and in two, after carbon monoxide intoxication. Such cases are often explained by the decrease in the resistance of the organism and activation of the infection, but the possibility cannot be forgotten of biochemical changes in the protein and the formation of autoantigens. In those suffering from rheumatic fever, the pains not uncommonly were more marked in those joints which were overworked. Frequently repeated small traumata lead to certain tissue changes, which tissues, after the action of various other factors, more rapidly acquire the properties of antigens.

With the extensive use of various therapeutic measures, we sometimes come into contact with increased sensitivity and a stormy reaction. N. Belyayeva and T. S. Kanevskaya have described cases of an acute hemolytic reaction to a therapeutic dose of streptocide. Evidently, drug hemolytic anemia and drug agranulocytosis develop in connection with the occurrence of anti-erythrocytic or anti-leucocytic immune globulins. It may also be considered entirely probable that injuries from the action of X-Rays are associated with the occurrence of denaturation processes in the proteins of the body.

Among the numerous pathogenetic factors, the nervous system has special significance; more than reflex reaction changes depend on it. Sensitization of the organism and humoral reactions are associated with higher nervous activity. A. A. Markosyan established the fact that painful stimuli

accelerate the coagulation of the blood. Kreniger and Guggenberger showed on more than 1000 mice that the course of an infection may be exacerbated by fear, and fatal relapses may be produced in bacillary carriers. Goretsky and Ludani found that toxins acting on the vegatative nervous system alter the titer of opsonins, agglutinins and precipitins. The numerous works of A. D. Speranskiy and his colleagues were devoted to proving that the chief link in each infection process is the central nervous system. V. Arutyunov noted, in patients suffering from lupus erythematosus, a deterioration of the disease process during traumatic experiences. Although certain authors deny the effect of the conditioned reflexes on the formation of antibodies, there can hardly be any doubt of the great role which the central nervous system plays in the immune hematological processes. Traumatic experiences and strong emotions not only lead to a collision of the stimulatory and inhibitory processes but also, in consequence of the impairment of function of the subcortial centers, vegetative nervous system and endocrine glands, contribute to the development of a "conflict" between the autoantigens and the autoantibodies and to the occurrence of various pathological changes.

Thus, the autoantigens are formed in connection with the disturbance of function of the nervous system and the action of various environmental factors. In this group are infections, toxins, low and high temperatures, trauma, X-Rays, and sometimes also certain drugs. Undoubtedly, there are many other factors the role of which has not been studied to date. If, in consequence of the action of any single harmful factor among a multitude of persons, pathological changes occur only in some of them, it may be supposed that the occurrence of autoantigens and autoantibodies is associated with a combination of several factors, part of which still remain unexplained.

Of the agents which counteract sensitization, ACTH and cortisone are most often used. Anti-inflammatory and desensitizing agents, like the salicylates and other preparations, have a certain significance. Blood transfusions is also being used with some success. Liver extract and vitamin B_{12} have a secondary significance.

Of the surgical methods in the therapy of thrombopenia, hemolytic anemia and certain other diseases splenectomy is used. Lopez Cardozo published a case of lupus erythematosus where a stable remission was obtained after the removal of the spleen. However, as is well known, the spleen is not

the only organ involved in the formation of antibodies and only a temporary remission is not uncommonly observed after the operation.

The results achieved in the therapy of diseases, in the pathogenesis of which the autoagressors play an appropriate role are still unsatisfactory. Even one of the best measures against sensitization of the body--ACTH--sometimes can produce drug-induced disease itself. Only the subsequent study of the causes leading to the formation of autoantigens and autoantibodies can improve the therapy and prophylaxis of a number of serious diseases.

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